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| EXAMINER | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/759,256 | CONSEILLER ET AL. | |
| | Examiner | Art Unit | |
| | Brad Duffy | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *06 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *31-97* is/are pending in the application.

4a) Of the above claim(s) *32,34 and 36-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Ex. A,B and Notice to Comply*.

## DETAILED ACTION

1. The election with traverse filed March 6, 2007 is acknowledged and has been entered.

Applicant has elected the invention of Group II, claims 33 and 35, drawn to polypeptides comprising all or part or SEQ ID NO:31 or SEQ ID NO:22, or a derivative thereof. Furthermore, linking claim 31 will be examined with the elected invention.

2. Claims 31-97 are pending in the application.

3. Claims 32, 34 and 36-97 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 6, 2007.

4. Claims 31, 33 and 35 are under examination.

### *Response to Amendment*

5. The amendment filed on January 20, 2004, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment[1], Applicant is advised to correct the following deficiency in replying to this Office action:

The amendment to the claims is non-compliant because the listing of claims does not begin on a separate sheet and does not properly indicate the status of each of the claims.

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[1] See M.P.E.P. § 714.03.

Also - The amendment to the specification is non-compliant because it does not commence on a separate page.

Briefly, the revised amendment practice now requires a listing of all claims beginning on a separate sheet. Each claim ever presented must be included in the listing of claims together with a single proper status identifier in parentheses. The permissible status identifiers include: "original", "currently amended", "canceled", "withdrawn", "previously presented", "new", and "not entered". The text of all pending claims, including withdrawn claims, must be presented. Markings to show only the changes made in the current amendment relative to the immediate prior version should be included with the text of all currently amended claims, including withdrawn claims that are amended. Added text must be shown by underlining the added text. Generally deleted text must be shown by strikethrough (e.g., ~~strikethrough~~); or if the strikethrough cannot be easily perceived, and for deletion of five or fewer characters, the deleted text may be marked by the inclusion of deleted text in double brackets (e.g., [[444]]). The text of "canceled" and "not entered" claims must not be presented; and consecutive "canceled" or "not entered" claims may be grouped together in one line (e.g., Claims 1-11 (canceled); Claims 51-62 (not entered)).

Only the corrected section of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the specification" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

***Election/Restrictions***

6. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed September 6, 2006, is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

The traversal is on the grounds that, there would not be a serious burden in examining all the claims together. Contrary to Applicant's assertions, the inventions are patentably distinct for the reasons set forth in the Office action mailed September 6, 2006, and because they are so distinct, the search necessary to examine claims

directed to any one of the inventions is not the same, nor is it coextensive with the search required to examine claims directed to any other. Consequently, different searches must be performed to examine claims directed to each of the different groups of inventions; and a need to perform more than one search would constitute a serious burden.

Furthermore, Applicant has provided no evidence to establish why the remaining groups are sufficiently related or why the Groups are not distinct one form the others. Clearly different searches and issues are raised in the examination of each group, which would create a serious burden on the Office. See MPEP 808.02.

Therefore, since there would serious burden and the inventions are patentably distinct for the reasons set forth in the Office action mailed September 6, 2006, the requirement is still deemed proper and is therefore made FINAL.

***Information Disclosure Statement***

7. The references cited in the information disclosure statement filed on April 27, 2004, have been considered.

Notably, while the references on page 3 were considered this page fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609.

***Application Data Sheet***

8. The application data sheet is objected to as improperly claiming priority because it does not list an application to which priority is claimed in each row. Therefore it is unclear if, for example, the instant application is claiming priority to provisional application 60/132,331, or if the PCT is claiming priority to the provisional application. Applicant is required to file a "Supplemental Application Data Sheet to clarify the

intended priority claim. See 37 CFR 1.76 and MPEP § 601.05(c) for rules concerning "Supplemental Application Data Sheets".

***Priority***

9. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of applications 09/829,936, filed April 11, 2001, 60/132,331, filed April 23, 1998, PCT/FR99/02465, filed October 12, 1999 and FR 98/12754, filed October 12, 1998, is acknowledged.

However, claims 31, 33 and 35 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, the claims do not properly benefit under 35 USC §§ 119 and/or 120 by the earlier filing date of PCT/FR99/02465, filed October 12, 1999, or Provisional Application No. 60/132,331, filed April 23, 1998, because these applications do not describe polypeptides comprising the amino acid sequence of SEQ ID NO: 22. In this case the sequence of the human MBP1 polypeptide disclosed in the priority applications is different than the instant SEQ ID NO:22. Notably, the priority application list residue 396 of the human MBP1 polypeptide as Ser, while the instant SEQ ID NO:22 lists this residue as Phe.

Finally, while acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 10/12/98, it is noted that applicant has not

provided a certified copy of the French application as required by 35 U.S.C. 119(b).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely January 20, 2004.

***Drawings***

10. The drawings set forth as Figure 4A and 4B are objected to because they depict amino acid sequences, which are not identified by sequence identification numbers, either in the figure or in the Legend to the figures at page 26. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the figure at page 26 of the specification to include sequence identification numbers, provided that the amino acid sequences presented in the figures are the same as the sequences given in the respective SEQ ID NO.

***Specification***

11. The disclosure is objected to for the following reasons:

(a) The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified

amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figure 4A and 4B are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 26. Furthermore at least the human MBP1 sequence depicts a different amino acid sequence than SEQ ID NO:22 which is also referred to as human MBP1 at page 21 of the specification. Notably, the amino acid at position 396 is Phe in the sequence list, while Figure 4 indicates that position 396 is Ser.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

(b) The specification is objected to because the section that describes the drawings is labeled "Legend to the Figures" (see page 26 of the specification). The description of the drawings should be labeled, "Brief Description of the Drawings" See MPEP § 608.01(f). Furthermore, the specification is objected to because this section fails to comply with 37 CFR 1.84(p)(5) which requires every reference character to be described in the brief description. In this case, the description of Figure 4 does not refer to Figure 4A or Figure 4B.

(c) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be

respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such an improperly demarcated trademarks appearing in the specification include GenBank™ and SuperScript™ (see page 53 and 54).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

(d) The specification is objected to because the priority claim in the first paragraph, as amended January 20, 2004, is incorrect and unclear. This application appears to be a continuation of application 09/829936, which is a national stage of the PCT, which claims benefit of the provisional and foreign applications and therefore the current priority claim listed does not comply with 35 USC §§ 119 and/or 120.

(e) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 31, 33 and 35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 31, 33 and 35, as written, do not distinguish the claimed polypeptides from naturally occurring polypeptides because the claims do not particularly point out any non-naturally occurring differences between the claimed polypeptides and the structure of naturally occurring polypeptides. The claims read upon naturally-occurring polypeptides of the same structure.

In the absence of the hand of man, the naturally occurring polypeptides or compositions of matter are considered non-statutory subject matter. See *Diamond v. Chakrabadv*, 206 U.S.P.Q. 193 (1980)).

Amendment of the claims to recite the limitation "isolated" before "polypeptide", for example, would obviate this rejection.

14. Claims 31, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines"

continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

Claims 31, 33 and 35 are drawn to a genus of structurally and/or functionally diverse "polypeptides" capable of interacting specifically with the "oncogenic forms of p53", and capable of stimulating cell growth and capable of blocking the antiproliferative effects of the wild-type form of p53, wherein the polypeptides comprise all or part of the amino acid sequence of SEQ ID NO:31 or SEQ ID NO:22, or a derivative thereof or wherein the amino acid sequence consists of SEQ ID NO:22, or a derivative thereof.

Notably, claim 35 is interpreted as encompassing derivatives of polypeptides consisting of SEQ ID NO:22 as the polypeptide of claim 33 encompasses derivative polypeptides.

The specification discloses at page 11, that "polypeptide derivatives" includes

> "any polypeptide sequence differing from the sequence considered, which is obtained by one or more modifications of a genetic and/or chemical nature, and possessing the capacity to interact with the oncogenic mutated forms of p53. Modification of a genetic and/or chemical nature is understood to mean any mutation, substitution, deletion, addition and/or modification of one or more residues. Such derivatives may be generated for different objectives, such as in particular that of modifying their properties of binding to the oncogenic 25 mutated forms of P53, or of increasing their therapeutic efficacy or of reducing their side effects, or that of conferring on them new pharmacokinetic and/or biological properties."

Furthermore, at page 11, the specification discloses that polypeptide derivatives of SEQ ID NO:22 or SEQ ID NO:31 includes polypeptides with a low as 80% sequence identity to these polypeptides and fragments of these polypeptides.

Thus, the claims are broadly but reasonably directed to a genus of structurally and functionally diverse "polypeptides" that are only required to comprise 80% amino acid identity to a polypeptide comprising or consisting of SEQ ID NO:22 or comprising SEQ ID NO:31 as well as fragments of these polypeptides. However, the specification does not describe with the requisite particularity needed to provide adequate written description, any "polypeptides" comprising a polypeptide with 80% amino acid a polypeptide comprising or consisting of SEQ ID NO:22 or comprising SEQ ID NO:31 or fragments thereof that would still retain the function of the full-length protein, i.e. the polypeptide of SEQ ID NO:22.

Notably, in this case the specification does not provide any guidance as to which mutations, substitutions, deletions, additions and/or modifications of polypeptides comprising SEQ ID NO:22 or SEQ ID NO:31 or which "parts" of these polypeptides would retain the function of binding to oncogenic p53, stimulating cell-growth and blocking the antiproliferative effects wild-type p53 so as to allow one of skill in the art to immediately envision, recognize or distinguish the claimed polypeptides from any others; and therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Additionally, the specification does not provide any guidance as to which amino acids could be altered in polypeptides comprising SEQ ID NO:22 or SEQ ID NO:31 to arrive at polypeptides with at least 80% amino acid identity or fragments thereof so that the claimed polypeptides would retain the function of the polypeptide full-length polypeptide of SEQ ID NO:22. In this case, specific guidance is needed to provide adequate support for the genus of the "derivatives" and "parts" of SEQ ID NO:22 or SEQ ID NO:31 because it is well-established in the art that there is a high degree of unpredictability in determining the three-dimensional structure of a given protein *a priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure.

As evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133, 3rd paragraph). Furthermore, Tosatto et al state, "the link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Therefore, the structure and function of the "derivatives" and "parts" of SEQ ID NO:22 or SEQ ID NO:31 is highly unpredictable given the disclosure of the polypeptide of SEQ ID NO:22.

Thus, not all the polypeptides comprising sequences that would be considered "derivatives" and "parts" of SEQ ID NO:22 or SEQ ID NO:31, are reasonably expected to have a function that is equivalent to the function of the polypeptide of SEQ ID NO: 22.

In support of this conclusion, Skolnick et al. (*Trends in Biotechnology* 2000; 18: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

In addition, Bowie et al. (*Science* 257: 1306-1310, 1990) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of all the possible proteins and fragments, which fall within the scope of the claims, the skilled artisan could not recognize which of these would function similarly to the protein of SEQ ID NO: 22, and which would not.

Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a polypeptide that comprises a sequence with 80% identity to a polypeptide comprising SEQ ID NO: 22 or SEQ ID NO:31 or fragments thereof is functionally equivalent to the polypeptide of SEQ ID NO: 22, or even has a structure that is substantially equivalent to that of the polypeptide of SEQ ID NO: 22.

Furthermore, where the claims are drawn to "oncogenic forms" of p53, it is noted that the specification only adequately describes an arginine to histidine mutation at position 175 of p53 as an "oncogenic form of p53" to which polypeptides comprising SEQ ID NO:22 specifically bind (see Figure 2 and Example 4 starting on page 38). Notably, for similar reasons outlined above so as to explain that one of skill in the art would not immediately envision which "derivatives" of SEQ ID NO:22 would retain the stated function of the full-length protein, one of skill in the art would also not immediately envision which mutations in p53 are "oncogenic" or even if an "oncogenic form" of p53 would necessarily retain the ability to bind polypeptides comprising SEQ ID NO:22 as the "oncogenic mutation" could easily alter p53 binding specificity.

Accordingly, the genus of "polypeptides" capable of interacting specifically with the "oncogenic forms" of p53, and capable of stimulating cell growth and capable of blocking the antiproliferative effects of the wild-type form of p53, wherein the polypeptides comprise all or part of the amino acid sequence of SEQ ID NO:31 or SEQ

ID NO:22, or a derivative thereof or wherein the amino acid sequence consists of SEQ ID NO:22, or a derivative thereof" includes members, having substantially and significantly variant structures and/or functions. The specification fails to adequately describe this genus, as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other polypeptides, as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those polypeptides.

The description of the amino acid sequence of SEQ ID NO:22 and SEQ ID NO:31 is not representative of the entire genus because the genus is highly variable, inclusive to a variety of structurally undefined "polypeptides" that are also functionally diverse. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In addition, although the skilled artisan could potentially make a list with every polypeptide having 80% homology to SEQ ID NO:22 or SEQ ID NO:31 and fragments thereof as encompassed by the claims and contemplated in the specification, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Applicant is reminded "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69

USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of polypeptides comprising sequences that would be considered "derivatives" and "parts" of SEQ ID NO:22 or SEQ ID NO:31, because there is no particularly identifying structural feature that correlates with the stated function of specifically binding oncogenic p53, stimulating cell growth and blocking the antiproliferative effects of the wild-type form of p53. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Given the lack of particularity with which the "derivatives" and "parts" of SEQ ID NO:22 or SEQ ID NO:31 which are capable of binding "oncogenic forms" of p53, to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of polypeptides to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). In this case, because the claims encompass a genus of "polypeptides having at least 80% identity to polypeptides comprising SEQ ID NO: 22 or SEQ ID NO:33 and fragments thereof", which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or

structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

15. Claims 31, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a polypeptide comprising SEQ ID NO:22 or polypeptides consisting of a fragment of the polypeptide of SEQ ID NO: 22, and **while being enabling for making and using** any polypetides encompassed by the claims disclosed in the prior art **does not reasonably provide enablement for making and using** any and all polypeptides, either whole or in part capable of interacting specifically with any oncogenic form of p53, and capable of stimulating cell growth, and capable of blocking the antiproliferative effects of the wild-type form of p53 and **does not reasonably provide enablement for making and using** polypeptide derivatives of SEQ ID NO:22 or its parts or polypeptides comprising fragments of SEQ ID NO:22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the full scope of the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The specification teaches that mouse and human MBP1 polypeptides bind the oncogenic form of p53 with a histidine substitution at residue 175, and that these polypeptides are capable of stimulating cell growth and blocking the antiproiferative effects of wild-type p53 (see of page 8, lines 3-17, page 9, lines 1-7 and 18-28 and figure 2 and 5). The specification also teaches that the human MPB1 full-length protein consists of SEQ ID NO:22 (see page 10, lines 1-5).

In this case claim 31 is drawn to a genus of polypeptides capable of interacting specifically with oncogenic forms of p53, and capable of stimulating cell growth, and capable of blocking the antiproliferative effects of the wild-type form of p53 and claims 33 and 35 are drawn to a genus of polypeptides comprising or consisting of SEQ ID NO:22 or comprising SEQ ID NO:31 or derivatives and/or fragments thereof of these polypeptides.

As noted in the above written description rejection, the specification does not provide any guidance as to which derivatives or polypeptides comprising fragments of SEQ ID NO:22 would retain the requisite abilities to interact specifically with oncogenic forms of p53, and would be able to stimulate cell growth and would be capable of blocking the antiproliferative effects of the wild-type form of p53. The applicant has not provided any working examples of any "derivatives" or "fragments" of SEQ ID NO:22

that still interact with the histidine 175 substitution form of p53 with these abilities. Therefore the applicant has not demonstrated which amino acids in the protein's sequence are tolerant of modification and which amino acids need to be conserved to retain these functions nor which fragments of the full-length protein would be expected to retain these functions.

Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a polypeptide "derivative" of SEQ ID NO: 22 or a polypeptide comprising a "fragment" of SEQ ID NO: 22 is functionally equivalent to the polypeptide of SEQ ID NO: 22, or even has a structure that is substantially equivalent to that of the polypeptide of SEQ ID NO: 22.

Furthermore, while the skilled artisan cannot reliably and accurately predict the functional and structural consequences of amino acid differences it is known that the more structurally disparate a given protein, the less likely the protein will share the function of structurally related proteins having known functions. Burgess et al. (*Journal of Cell Biology* 1990; **111**: 2129-2138) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of this sensitivity to amino acid sequence variations, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein.

Echoing this fact, Takada et al. (*Mol. Endocrinol.* 2000; **14** (5): 733-740) teaches that the lack of predictability in the art remains, despite technological advances and a better understanding of the structure-function relationship; see entire document (e.g., the abstract). Takada et al. teaches their work illustrates that a single amino acid change may be sufficient to cause the acquisition of a new ligand binding specificity as

well as to suppress recognition of a previous ligand, extending observations by others who showed that changes in one or several amino acids can result in marked alterations in activity and function of nuclear receptors (page 738, column 1). Notably, Takada et al. teaches that the functional consequence of amino acid substitution may be rather subtle, since the variants of the receptors were still able to bind to the promoter of the reporter construct and activate transcription in the presence of some ligands but not others; see, e.g., page 739, Figure 5. Takada et al. teaches the difference in ligand binding specificity caused by the amino acid changes results in the variants having the activity of different member of the family of proteins; see, e.g., the abstract. Thus, Takada et al. discloses that seemingly subtle differences resulting from amino acid differences, such as changes in ligand binding specificity, may cause variants of a protein to have a function that differs markedly from that of the protein. Accordingly, depending upon the assay used to assess the activity of the proteins and its variants, the effects of amino acid sequence variation may not be immediately recognized or appreciated, since the variants may appear to function normally otherwise, but in actuality have substantially different functions.

Even more recently, Guo et al. (*Proc. Natl. Acad. Sci. USA.* 2004 Jun 22; **101** (25): 9205-9210) have calculated the probability that a random amino acid substitution, such as that which might occur naturally during aging or as a consequence of evolution or disease, will cause inactivation of a protein; see entire document (e.g., the abstract). Guo et al. reports this probability was found to be 34% ± 6% (abstract); that is, 34% of random mutations in the sequence of a protein are predicted to cause the inactivation of the protein. Guo et al. observed that various residues are differentially sensitive to substitutions, but the tolerance of the entire protein to random change can be defined by the probability that any given random amino acid substitution will inactivate the protein (i.e., the so-called "*x* factor") (page 9209, column 2). Not surprisingly, evolutionarily conserved residues showed low substitutability indices (abstract).

Thus, as evidenced by these references, it is even more apparent that the functional consequences of the amino acid differences must be ascertained before any given polypeptide "derivative" of SEQ ID NO: 22 or polypeptide comprising a "fragment"

of SEQ ID NO: 22 of a protein can be used in the same manner in which the protein having a known function is used.

Accordingly, because it cannot be predicted whether the polypeptide "derivatives" or "fragments" of SEQ ID NO: 22 would have the functional characteristics of the full-length protein and the specification lacks guidance as to which modifications could be made to make these "derivatives" or "fragments" of SEQ ID NO: 22 that would retain these functional characteristics so that the polypeptides could then be used, one of skill in the art would be subject to undue experimentation to make and use polypeptides commensurate in scope with the claims. For example, determining whether these undefined "polypeptides", "derivatives" or "fragments" have these functional characteristics, which is necessary before the invention can be used, constitutes additional, undue experimentation.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

### *Claim Rejections - 35 USC § 102*

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 31, 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (Molecular and Cellular Biology 13(7), 4107-4114, 1993, IDS filed April

27, 2004).

Claim 31 is drawn to a polypeptide that is capable of specifically interacting with oncogenic forms of p53, and capable of stimulating cell growth and capable of blocking the antiproliferative effects of the wild-type p53. While "oncogenic forms of p53" forms of p53 are not expressly defined by the specification, at page 8 the specification indicates that p53 with a histidine substitution at residue 175 is an oncogenic form of p53. Claims 33 and 35 are herein interpreted as being drawn to polypeptide derivatives of a polypeptide comprising all or part of SEQ ID NO: 22.

Chen et al teach a polypeptide designated Mdm2 that can specifically bind p53 with residue 175 substituted to histdine. (see entire document, e.g., abstract and page 4109, left column). Chen et al further teach that Mdm2 stimulates cell growth and is capable of blocking the antiproliferative effects of wild-type p53 (e.g., page 4107, left column and page 4112, right column). Therefore, since the Mdm2 polypeptide of Chen is materially and structurally indistinguishable from the claimed invention, so as to be expected to have identical functional features, it would be considered a derivative of a polypeptide comprising part of SEQ ID NO:22.

The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed invention. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the invention and the products disclosed by the prior art are different. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Furthermore, while "oncogenic forms of p53" forms of p53 are not expressly defined by the specification, at page 8 the specification indicates that p53 with a histidine substitution at residue 175 is an oncogenic form of p53.

Thus, Chen et al anticipate these claims.

18. Claims 31, 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Olsen et al (WO 97/38012, 1997, IDS filed April 27, 2004).

The claims are interpreted at being drawn to polypeptide derivatives of SEQ ID NO:22 or polypeptides comprising SEQ ID NO:31. Notably, the specification discloses at page 11 that sequences with at least 80% sequence identity would be considered derivatives of SEQ ID NO:22.

Olsen et al teach a polypeptide in Figure 1 of this reference comprising sequences 99.7% identical to SEQ ID NO:22 (see Exhibit A attached) and 100% identical to SEQ ID NO:31 (see exhibit B attached). Thus, the reference reads on the "derivative" of SEQ ID No. 22 and polypeptides comprising SEQ ID:31 and, absent a showing otherwise would inherently specifically bind oncogenic forms of p53, stimulate cell-growth and block the antiproliferative effects of the will-type form of p53.

Thus, Olsen et al anticipate these claims.

***Conclusion***

19. No claims are allowed.

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 5,916769 discloses a polypeptide 99.7% identical to the instant SEQ ID NO:22.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

STEPHEN L. RAWLINGS, PH.D.
PRIMARY EXAMINER

bd
April 24, 2007

Exhibit A

<!--StartFragment-->RESULT 1
AAW32110
ID  AAW32110 standard; protein; 443 AA.
XX
AC  AAW32110;
XX
DT  14-APR-1998  (first entry)
XX
DE  Human extracellular/epidermal growth factor HCABA58X.
XX
KW  Extracellular/epidermal growth factor; HCABA58X; human;
KW  ss. vascular smooth muscle proliferation; Marfan syndrome; dementia;
KW  wound healing; alopecia; neurological disorder; ocular disorder;
KW  kidney disorder; liver disorder; embryogenesis; angiogenesis; antagonist;
KW  corneal inflammation; psoriasis; diabetes; therapy.
XX
OS  Homo sapiens.
XX
PN  WO9738012-A1.
XX
PD  16-OCT-1997.
XX
PF  10-APR-1996;  96WO-US005033.
XX
PR  10-APR-1996;  96WO-US005033.
XX
PA  (HUMA-) HUMAN GENOME SCI INC.
XX
PI  Olsen HS,  Ruben SM;
XX
DR  WPI; 1997-512646/47.
DR  N-PSDB; AAT88974.
XX
PT  DNA encoding extracellular-epidermal growth factor HCABA58X - useful for
PT  treatment and diagnosis of e.g. wounds, neurological disease, neoplasia,
PT  psoriasis etc.
XX
PS  Claim 11; Fig 1; 47pp; English.
XX
CC  This human polypeptide, designated HCABA58X, was identified on the basis
CC  of homology as an extracellular protein-like/epidermal growth factor-like
CC  protein. Its amino acid sequence was deduced from a cDNA clone (see
CC  AAT88974) isolated from an osteoclastoma cDNA library, and shows 51%
CC  identity and 30% similarity to human extracellular protein. Recombinant
CC  HCABA58X polypeptides (the polypeptide comprising amino acids 1-419 is
CC  also claimed) can be expressed in bacterial, insect, mammalian or plant
CC  cells. The polypeptides, and polynucleotides encoding them, can be used
CC  e.g. to induce DNA synthesis, to regulate vascular smooth muscle
CC  proliferation, to treat Marfan syndrome, to stimulate wound healing, to
CC  restore normal neurological function after trauma or AIDS dementia, to
CC  treat ocular disorders, to treat kidney and liver disorders, to promote
CC  hair follicular development, to stimulate growth and differentiation of
CC  epidermal and epithelial cells in vivo and in vitro, for the treatment of
CC  burns, ulcers and corneal incisions, and to stimulate embryogenesis and
CC  angiogenesis. They can also used to identify antagonists (used e.g. to
CC  treat corneal inflammation, neoplasia, tumours, cancers and psoriasis)
CC  and agonists, and to raise diagnostic antibodies
XX
SQ  Sequence 443 AA;

  Query Match             99.7%;  Score 2505;  DB 2;  Length 443;
  Best Local Similarity   99.8%;  Pred. No. 3.8e-133;
  Matches  442;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

```
Qy          1 MLPCASCLPGSLLLWALLLLLLGSASPQDSEEPDSYTECTDGYEWDPDSQHCRDVNECLT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MLPCASCLPGSLLLWALLLLLLGSASPQDSEEPDSYTECTDGYEWDPDSQHCRDVNECLT 60

Qy         61 IPEACKGEMKCINHYGGYLCLPRSAAVINDLHGEGPPPPVPPAQHPNPCPPGYEPDDQDS 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 IPEACKGEMKCINHYGGYLCLPRSAAVINDLHGEGPPPPVPPAQHPNPCPPGYEPDDQDS 120

Qy        121 CVDVDECAQALHDCRPSQDCHNLPGSYQCTCPDGYRKIGPECVDIDECRYRYCQHRCVNL 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 CVDVDECAQALHDCRPSQDCHNLPGSYQCTCPDGYRKIGPECVDIDECRYRYCQHRCVNL 180
```

```
Qy        181 PGSFRCQCEPGFQLGPNNRSCVDVNECDMGAPCEQRCFNSYGTFLCRCHQGYELHRDGFS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 PGSFRCQCEPGFQLGPNNRSCVDVNECDMGAPCEQRCFNSYGTFLCRCHQGYELHRDGFS 240

Qy        241 CSDIDECSYSSYLCQYRCVNEPGRFSCHCPQGYQLLATRLCQDIDECESGAHQCSEAQTC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 CSDIDECSYSSYLCQYRCVNEPGRFSCHCPQGYQLLATRLCQDIDECESGAHQCSEAQTC 300

Qy        301 VNFHGGYRCVDTNRCVEPYIQVSENRCLCPASNPLCREQPSSIVHRYMTITSERSVPADV 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 VNFHGGYRCVDTNRCVEPYIQVSENRCLCPASNPLCREQPSSIVHRYMTITSERSVPADV 360

Qy        361 FQIQATSVYPGAYNAFQIRAGNSQGDFYIRQINNVFAMLVLARPVTGPREYVLDLEMVTM 420
              |||||||||||||||||||||||||||||||| ||||||||||||||||||||||||||
Db        361 FQIQATSVYPGAYNAFQIRAGNSQGDFYIRQINNVSAMLVLARPVTGPREYVLDLEMVTM 420

Qy        421 NSLMSYRASSVLRLTVFVGAYTF 443
              |||||||||||||||||||||||
Db        421 NSLMSYRASSVLRLTVFVGAYTF 443
<!--EndFragment-->
```

Exhibit B

<!--StartFragment-->RESULT 3
AAW32110
ID  AAW32110 standard; protein; 443 AA.
XX
AC  AAW32110;
XX
DT  14-APR-1998  (first entry)
XX
DE  Human extracellular/epidermal growth factor HCABA58X.
XX
KW  Extracellular/epidermal growth factor; HCABA58X; human;
KW  ss. vascular smooth muscle proliferation; Marfan syndrome; dementia;
KW  wound healing; alopecia; neurological disorder; ocular disorder;
KW  kidney disorder; liver disorder; embryogenesis; angiogenesis; antagonist;
KW  corneal inflammation; psoriasis; diabetes; therapy.
XX
OS  Homo sapiens.
XX
PN  WO9738012-A1.
XX
PD  16-OCT-1997.
XX
PF  10-APR-1996;  96WO-US005033.
XX
PR  10-APR-1996;  96WO-US005033.
XX
PA  (HUMA-) HUMAN GENOME SCI INC.
XX
PI  Olsen HS,  Ruben SM;
XX
DR  WPI; 1997-512646/47.
DR  N-PSDB; AAT88974.
XX
PT  DNA encoding extracellular-epidermal growth factor HCABA58X - useful for
PT  treatment and diagnosis of e.g. wounds, neurological disease, neoplasia,
PT  psoriasis etc.
XX
PS  Claim 11; Fig 1; 47pp; English.
XX
CC  This human polypeptide, designated HCABA58X, was identified on the basis
CC  of homology as an extracellular protein-like/epidermal growth factor-like
CC  protein. Its amino acid sequence was deduced from a cDNA clone (see
CC  AAT88974) isolated from an osteoclastoma cDNA library, and shows 51%
CC  identity and 30% similarity to human extracellular protein. Recombinant
CC  HCABA58X polypeptides (the polypeptide comprising amino acids 1-419 is
CC  also claimed) can be expressed in bacterial, insect, mammalian or plant
CC  cells. The polypeptides, and polynucleotides encoding them, can be used
CC  e.g. to induce DNA synthesis, to regulate vascular smooth muscle
CC  proliferation, to treat Marfan syndrome, to stimulate wound healing, to
CC  restore normal neurological function after trauma or AIDS dementia, to
CC  treat ocular disorders, to treat kidney and liver disorders, to promote
CC  hair follicular development, to stimulate growth and differentiation of
CC  epidermal and epithelial cells in vivo and in vitro, for the treatment of
CC  burns, ulcers and corneal incisions, and to stimulate embryogenesis and
CC  angiogenesis. They can also used to identify antagonists (used e.g. to
CC  treat corneal inflammation, neoplasia, tumours, cancers and psoriasis)
CC  and agonists, and to raise diagnostic antibodies
XX
SQ  Sequence 443 AA;

  Query Match             100.0%;  Score 1653;  DB 2;  Length 443;
  Best Local Similarity   100.0%;  Pred. No. 2.6e-100;
  Matches  295;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

```
Qy          1 CTCPDGYRKIGPECVDIDECRYRYCQHRCVNLPGSFRCQCEPGFQLGPNNRSCVDVNECD 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        149 CTCPDGYRKIGPECVDIDECRYRYCQHRCVNLPGSFRCQCEPGFQLGPNNRSCVDVNECD 208

Qy         61 MGAPCEQRCFNSYGTFLCRCHQGYELHRDGFSCSDIDECSYSSYLCQYRCVNEPGRFSCH 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        209 MGAPCEQRCFNSYGTFLCRCHQGYELHRDGFSCSDIDECSYSSYLCQYRCVNEPGRFSCH 268

Qy        121 CPQGYQLLATRLCQDIDECESGAHQCSEAQTCVNFHGGYRCVDTNRCVEPYIQVSENRCL 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        269 CPQGYQLLATRLCQDIDECESGAHQCSEAQTCVNFHGGYRCVDTNRCVEPYIQVSENRCL 328
```

```
Qy        181 CPASNPLCREQPSSIVHRYMTITSERSVPADVFQIQATSVYPGAYNAFQIRAGNSQGDFY 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        329 CPASNPLCREQPSSIVHRYMTITSERSVPADVFQIQATSVYPGAYNAFQIRAGNSQGDFY 388

Qy        241 IRQINNVSAMLVLARPVTGPREYVLDLEMVTMNSLMSYRASSVLRLTVFVGAYTF 295
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        389 IRQINNVSAMLVLARPVTGPREYVLDLEMVTMNSLMSYRASSVLRLTVFVGAYTF 443
<!--EndFragment-->
```

| Notice to Comply | Application No. 10/759,256 | Applicant(s) CONSEILLER ET AL. | |
|---|---|---|---|
| | Examiner Brad Duffy | Art Unit 1643 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.

☒ 7. Other: The sequence of human MBP1 given in figure 4 differs from SEQ ID NO:22(also referred to as human MBP1). Applicant must clarify which sequence is correct for human MBP1 and make apporpriate corrections to the specification and/or the sequence listing.

### Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
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